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Predicted Economic Benefits of a Novel Biomarker for Earlier Sepsis Identification and Treatment: A Counterfactual Analysis

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Objectives: To estimate the potential clinical and health economic value of earlier sepsis identification in the emergency department using a novel diagnostic marker, monocyte distribution width.

Design: The analysis was conducted in two phases: 1) an analysis of the pivotal registration trial evidence to estimate the potential benefit of monocyte distribution width for early sepsis identification and (2) a cost-consequence analysis to estimate the potential economic and clinical benefits that could have resulted from earlier administration of antibiotics for those patients.

Setting: Sepsis identified in the emergency department which led to inpatient hospitalizations.

Patients: Adult sepsis patients admitted through the emergency department.

Interventions: None. This was a model simulation of clinical and economic outcomes of monocyte distribution width based on results from a noninterventional, multicenter clinical trial.

Measurements and Main Results: Among the 385 patients with sepsis, a total of 349 were eligible for inclusion. Sixty-seven percent of patients were predicted to benefit from monocyte distribution width results, resulting in an estimated mean reduction in time to antibiotics administration from 3.98 hours using standard of care to 2.07 hours using monocyte distribution width + standard of care. Based on this simulated reduction in time to antibiotics, monocyte distribution width + standard of care could have resulted in a less than or equal to 14.2% reduction (27.9% vs 32.5%) in mortality, a mean reduction of 1.48 days (10.0 vs 11.5 d) in length of stay, and $3,460 ($23,466 vs $26,926) savings per hospitalization. At the hospital level, based on an established national mean of 206 sepsis hospitalizations per hospital per year, earlier identification with monocyte distribution width is predicted to result in a total of $712,783 in annual cost savings per hospital.

Conclusions: Improved early identification of sepsis using monocyte distribution width along with current standard of care is estimated to improve both clinical and economic outcomes of sepsis patients presenting in the emergency department. Further research is warranted to confirm these model projections.

Key Words: antibiotics; cost analysis; costs; early treatment; performance improvement; sepsis

As the leading cause of death in hospitals in the United States, improved detection and treatment of sepsis is a leading worldwide healthcare priority (1). Annually, ~1.7 million adults in the United States are hospitalized for sepsis with ~270,000 deaths (2). Furthermore, sepsis is a major economic burden (3) as it is the most costly U.S. inpatient disease with more than $24 billion spent in 2013 alone (4). A critical component is prompt recognition and administration of antibiotics (5, 6). Although the Surviving Sepsis Campaign guidelines have been updated over time, the recommendation for initiating antibiotics within 2 hours has consistently been supported (7). Further, the Severe Sepsis and Septic Shock Management Bundle (SEP-1), created in 2015 by the Centers for Medicare and Medicaid Services, is the first national quality measure for early management of sepsis and recommends antibiotics within 3 hours of presentation of severe sepsis (8).

Delays in antibiotic administration are associated with greater in-hospital mortality (9–13) and antibiotic administration decreases the likelihood of death by 7.6% per hour (13). Real-world interventions that enhanced early recognition and treatment of sepsis have demonstrated reduced severity and mortality (14–17). Although international guidelines and real-world evidence support the administration of antibiotics as quickly as possible, sepsis patients still do not receive antibiotics within SEP-1 recommended intervals (18). To address the pressing need for earlier sepsis identification, facilities have implemented protocols and clinical decision support (CDS) tools with variable results (15, 19, 20).

Monocyte distribution width (MDW) is a novel biomarker recently shown to detect sepsis in emergency department (ED) settings with good sensitivity and specificity (21, 22). MDW is specifically measured using the UniCel DxH 900 analyzer (Beckman Coulter, Brea, CA). Given that MDW is available during the initial ED encounter as a component of the complete blood count (CBC) with differential, it is logical to posit that MDW could expedite sepsis identification and administration of antibiotics. Although the clinical benefits of earlier time to antibiotics (TTA) have been studied, it is unclear what the health economic benefit would be. The limited evidence available suggests reduced TTA is associated with lower healthcare resource utilization including shorter length of stay (LOS) and time in the ICU (23). Due to the dearth of available health economic evidence of earlier sepsis identification, the objective of the study was to: 1) estimate the modifiable delays using the MDW + SOC and 2) simulate the potential economic benefit of earlier TTA among sepsis patients presenting in the ED using this new technology.

MATERIALS AND METHODS

Simulated Reduction in TTA With MDW

Pivotal Trial. A noninterventional pivotal trial was conducted at three large medical centers to assess the clinical value of MDW (22). The pivotal trial included patients who presented to the ED, remained in the hospital for at least 12 hours and were confirmed to have sepsis (based on independent double adjudication and arbitration if discordant) using Sepsis-2 definition.

Data used for this model was aggregated and de-identified in which no one patient can be individually identified, and therefore, no patient consent was required, and the study was institutional review board (IRB) exempt. The pivotal trial (22) was IRB approved as stated in the article.

Methods to Estimate MDW + SOC TTA. Data from the pivotal trial were used to estimate the values of three key model inputs.

1) The actual TTA for SOC. The TTA for each sepsis patient in the pivotal trial was calculated by subtracting the time of administration of antibiotics from the time the patient arrived in the ED. The mean TTA was then calculated.

2) The estimated proportion of patients who could have benefitted. Due to the noninterventional nature of the trial, a counterfactual methodology was constructed to estimate the proportion of sepsis patients that may benefit from MDW. It was anticipated that some sepsis patients will immediately receive antibiotics due to their overt signs (e.g., shock, high

fever) and symptoms (rigors, purulent drainage) and, thus, will not be identified via MDW. Therefore, the proportion of sepsis patients that would benefit from MDW was estimated based on two key factors: a) a positive MDW test result (> 20) and b) administration of antibiotics after their healthcare provider would have received the MDW test result as a component of the initial CBC (the timing of which was documented). Due to the paucity of data for the turnaround of CBC results in a real-world setting, we assumed it would take 30 minutes for the healthcare provider to obtain the accompanying MDW test result (i.e., from the time the CBC was ordered, as entered in the patient's medical record). Scenario analyses were conducted for longer turnaround time assumptions of 45 minutes or 60 minutes.

3) The simulated weighted mean TTA for MDW + SOC. In the MDW + SOC arm of the model, the mean TTA was calculated among two populations: those assumed to be identified via MDW and those assumed to not be identified via MDW. To simulate the effect of MDW + SOC, if the two factors outlined above (a and b) were satisfied, the sepsis patient was counterfactually assigned a new TTA based on the availability of the MDW test result. The mean TTA was then recalculated among sepsis patients who could have benefitted from MDW to guide their therapy. The weighted mean TTA of the two groups (**Fig. 1**) was calculated to represent the mean TTA for MDW in the model.

Cost-Consequence Analysis

Model Design. A cost-consequence analysis from a hospital perspective (**Table 1**) was undertaken using a deterministic decision tree to estimate the potential health economic benefit of using MDW + SOC versus SOC alone over a time horizon representing the hospitalization period (Fig. 1). The key tenet of our analysis was simply to compare the outcomes of interest (i.e., costs, mortality rate, and LOS) between MDW + SOC versus SOC alone. A cost-consequence analysis was selected since researchers have noted that this approach is considered more approachable, more readily understood, and more commonly applied by U.S. healthcare decision-makers compared with more traditional cost-effectiveness analyses (24). Traditional cost-effectiveness analyses are designed to provide an incremental cost-effectiveness ratio, which is calculated by dividing the incremental cost of one healthcare technology option over another (e.g., a new technology compared with standard of care). The incremental difference in effect is typically reported in quality-adjusted life years (25). This incremental estimate of cost-effectiveness is more commonly used globally but rarely used in the United States for insurance coverage decisions.

Model Inputs. The model uses data from the literature and post hoc analysis of the clinical evidence described above. The model inputs are outlined in **Table 2**. The model is based on a mathematical relationship between TTA and the outcomes of interest. To estimate the clinical and economic benefits of reducing TTA, evidence on the relationship of TTA and the outcomes was identified from observational literature. Ferrer et al (23) stratified the unadjusted in-hospital mortality rate and LOS by TTA. We assumed 0–1, 1–2, 2–3, 3–4, 4–5, 5–6, and 6+ hours to be equal to 1, 2, 3, 4, 5, 6, and 7 hours, respectively. From the scatter plot, a best-fit
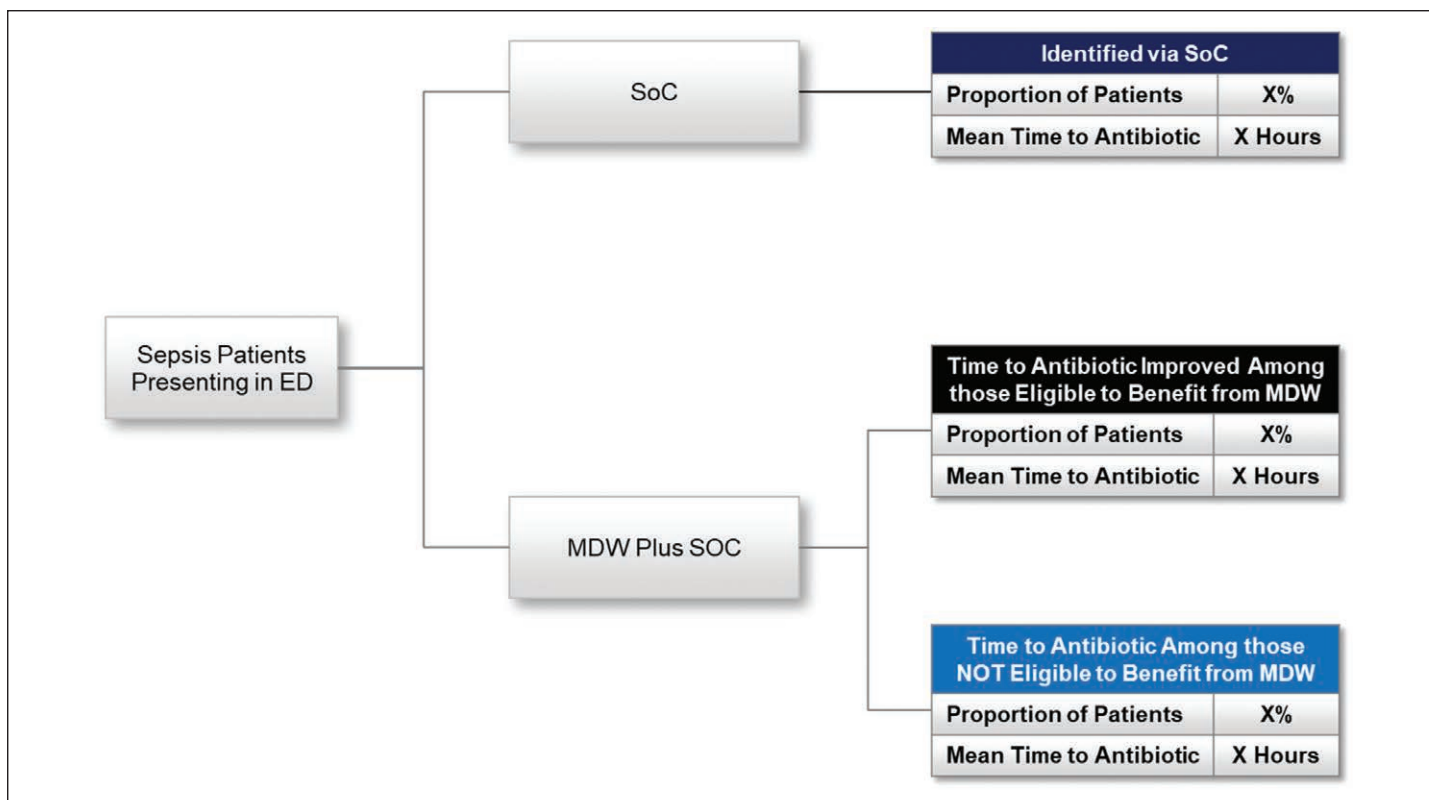
Figure 1. Cost-consequence analysis structure. ED = emergency department, MDW = monocyte distribution width, SOC = standard of care.

TABLE 1. Cost-Consequence Model Input Overview

Overview	Description
Design	Cost-consequence analysis using a deterministic decision tree
Intervention	Novel MDW biomarker
Comparator	SOC
Population	Sepsis patients presenting in the emergency department
Perspective	Costs over the hospitalization period
Sources	Pivotal clinical trial
	Published observational research
	Public cost databases
Inputs	Mean time to antibiotic for SOC
	Simulated mean weighted time to antibiotic for MDW
	Relationship of time to antibiotic and mortality
	Relationship of time to antibiotic and length of stay
	Cost per hospital day for a sepsis hospitalization
Outcomes	Absolute estimates and differences for MDW + SOC vs SOC
	Outcomes include costs, mortality rate, and length of stay

MDW = monocyte distribution width, SOC = standard of care.

linear regression was plotted to determine the slope of the line. This equation was then used to estimate outcomes for each arm. It is important to note that 1 hour and 6+ hours were not included in the equation as the data from Ferrer et al (23) resulted in a J-shaped curve. From a clinical perspective, it is likely that patients who received antibiotics during the first hour demonstrated overt signs and symptoms of severe sepsis or septic shock. Further, there were no hour-specific data provided by Ferrer et al (23) that corresponded to patients receiving antibiotics after 6 hours. The regression equations used to estimate the relationship between TTA and the outcomes of interest are illustrated in **Figure 2**. As described subsequently, scenario analyses were completed using the adjusted in-hospital mortality rate reported in the study by Ferrer et al (23) and also using the comparable rate reported in a similarly published study (29) to test the robustness of our findings.

Additional inputs included using 2015 National Inpatient Sample (NIS) data to estimate the mean cost of a sepsis hospitalization using the weighted average of hospitalization costs for the three diagnosis-related group (DRG) per codes associated with sepsis (870, 871, and 872) (26). The mean cost per day was calculated by dividing the weighted mean hospitalization costs by the weighted mean LOS across the three DRG codes. The mean cost per day was estimated to be $2,154 among those hospitalized for sepsis. When inflation adjusted using the medical care consumer price index from the Bureau of Labor Statistics (first half of 2018 relative to first half of 2015 = 1.09), the resulting inflation-adjusted cost per day was $2,344 per sepsis hospitalization day (27). To estimate the hospital-level impact, the mean number of

TABLE 2. Model Inputs

| Model Input	Base Case Value	Source
Time to MDW test	30 min	Input from key opinion leader
Mean time to antibiotic for standard of care	3.98	Trial data (22)
Simulated mean weighted time to antibiotic for MDW	1.34	Simulated based on trial data
Relationship of time to antibiotic and mortality	$y = 0.0241x + 0.2291$	Ferrer et al (23)
Relationship of time to antibiotic and length of stay	$y = 0.7714x + 8.4143$	Ferrer et al (23)
Cost per hospital day for a sepsis hospitalization	$2,541	Healthcare Cost and Utilization Project (26) and Bureau of Labor Statistics (27)
Number of sepsis admissions per hospital per year	206	Healthcare Cost and Utilization Project (26) and American Hospital Association (28)

MDW = monocyte distribution width.
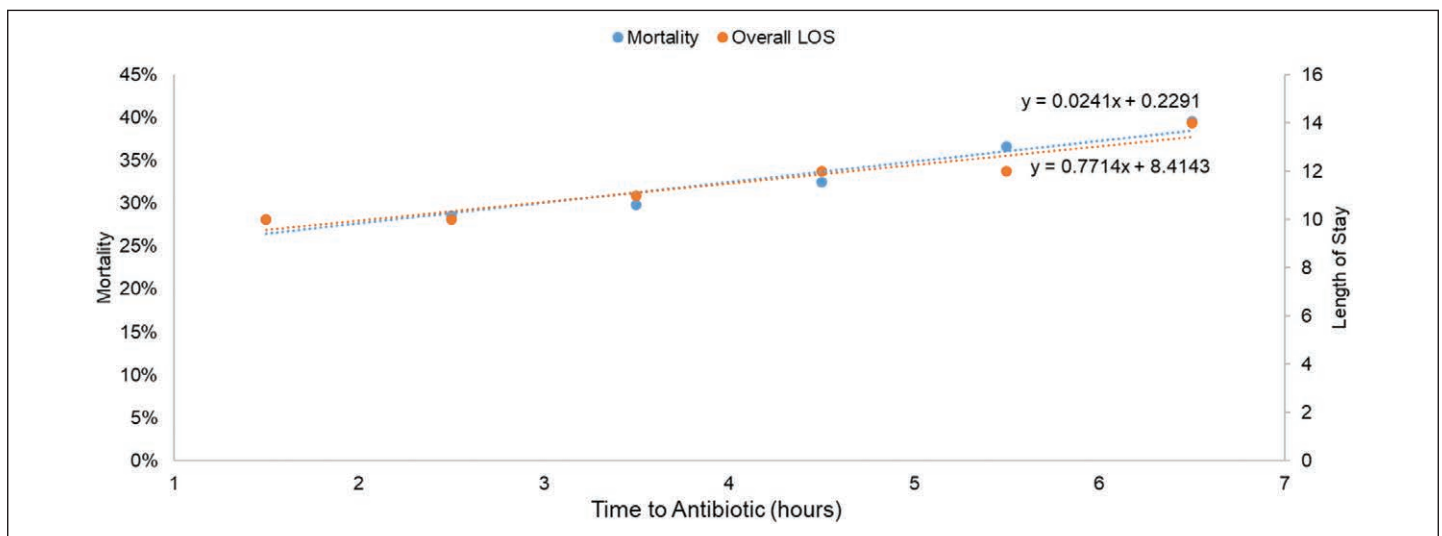
Figure 2. Relationship between time to antibiotic and outcomes of interest (Ferrer et al [23]). LOS = length of stay.

sepsis hospitalizations per year per hospital was calculated using 2015 NIS data and American Hospital Association data (26, 28). The number of sepsis-related hospitalizations identified based on the three DRG codes associated with sepsis was divided by the number of hospitals in the United States. Nationally, a total of 1,141,405 sepsis hospitalizations were observed out of a total of 5,534 hospitals, yielding an estimated 206 sepsis admissions per hospital per year for the base case analysis. As outlined further in a subsequent section, scenario analyses were then conducted to estimate the economic benefit among small and large hospitals.

Analysis and Outcomes

Base Case Analysis. The key outcomes of interest in this cost-consequence analysis comparing MDW + SOC versus SOC were the in-hospital mortality rate, mean hospital LOS, and the mean sepsis-related hospitalization costs. The analysis was conducted by applying the actual and simulated TTA for SOC and MDW + SOC, respectively, to the mathematical equations described in Figure 2. The in-hospital mortality rate as well as mean LOS and costs per sepsis hospitalization were calculated using the mean TTA observed for SOC and the simulated MDW + SOC. To calculate

the mean costs associated with a sepsis hospitalization, the mean cost per day was multiplied by the estimated mean LOS. The hospital-level analysis was executed by extrapolating the patient-level results to represent the results at an average-sized hospital over the course of a calendar year. The main outcomes of interest were the annual sepsis-related costs per hospital, annual number of sepsis-related days in the hospital, and annual number of sepsis-related in-hospital deaths for both the SOC and MDW + SOC arms.

Scenario Analyses. We conducted three independent scenario analyses while varying one single input for each. The three scenarios tested were 1) time from phlebotomy to antibiotics administration, 2) the size of the hospital, and 3) the effect of the relationship between the TTA and LOS and mortality. These three scenarios were tested one at a time. All base case inputs were set back to the default before conducting the next analysis (e.g., TTA was set back to 30 min before varying the size of the hospital).

One key model assumption was the time it would have taken for healthcare providers to obtain the MDW test result and start antibiotics. The base case analysis assumed it would take 30 minutes. However, it is understood that 30 minutes may not be realistic in all cases. Therefore, the scenario analysis tested the robustness of

TABLE 3. Time to Antibiotic for Standard of Care and Simulated Monocyte Distribution Width Benefits

Variables	All Sites
Standard of care mean (median) TTA (hr) for sepsis patients	3.98 (3.30) ($n = 349$)
Proportion of sepsis patients who received antibiotics after complete blood count time stamp + 30 min (when provider would have received MDW results)	90.0% ($n = 314$)
Proportion of sepsis patients who had a positive MDW (> 20)	74.24% ($n = 259$)
Proportion of sepsis patients who satisfy both requirements and may benefit from MDW	66.8% ($n = 233$)
MDW mean (median) TTA (hr) for sepsis patients	1.34 (1.15)

MDW = monocyte distribution width, TTA = time to antibiotics.

the results of phlebotomy to MDW result and to antibiotic administration intervals were 45 or 60 minutes.

We also tested the impact at the hospital level as the assumption of 206 sepsis admissions per hospital per year was based on a simple average. The economic benefit of adding MDW to SOC for small and large hospitals was based upon scenario analyses adjusted for a small hospital (< 100 beds, 108 sepsis hospitalizations annually) and a large hospital (≥ 500 beds, 1,024 sepsis hospitalizations annually).

The data from the article by Ferrer et al (23) used to estimate the relationship between mortality and LOS were unadjusted for severity because the severity-adjusted data for LOS were not reported; therefore, we conducted a scenario analysis using the adjusted in-hospital mortality rate. Because the patients in the study by Ferrer et al (23) had very advanced disease (> 60% in septic shock), we also conducted a scenario analysis using data from the study by Seymour et al (29) which all sepsis patients were admitted through the ED. We followed the same methodology by plotting a best-fit linear regression to determine the slope of the line. The regression equations were calculated to be y = 0.0143x + 0.2279 and y = 0.0043x + 0.2269 for Ferrer et al–adjusted (23) and Seymour et al (29), respectively. Once the mortality rates were calculated for SOC and MDW + SOC, we then applied the same observed reduction in the mortality to the LOS (since adjusted LOS data were not available in either article).

RESULTS

Pivotal Trial Analysis of SOC and MDW TTA

The population included in the pivotal trial was 51% female with a mean age of 61 years (22). Based on the required variables needed to estimate the potential MDW benefits, 349 of the 385 patients were used to populate the model. There were 36 patients excluded due to no antibiotics being given.

The mean TTA for SOC ($n = 349$) was 3.98 hours. As listed in **Table 3**, 66.8% satisfied both requirements and were estimated to potentially benefit from MDW based on an estimated mean TTA of 1.34 hours ($n = 233$). The mean TTA among those estimated to not benefit from MDW was 3.53 hours ($n = 116$). Therefore, the simulated weighted mean TTA for MDW + SOC was 2.07 hours.

Cost-Consequence Analysis

Patient-level results are outlined in **Table 4**. Earlier identification and administration of antibiotics using MDW + SOC may result in an absolute reduction of in-hospital mortality of 4.6% among sepsis patients relative to SOC, a 16.5% reduction. Adding MDW may result in $3,460 savings per sepsis patient. The adoption of MDW may reduce hospital LOS by nearly 1.48 days versus the standard of care.

Based on a national mean of 206 sepsis-related hospitalizations per hospital per year, there may be an annual reduction of $712,783 in sepsis-related hospitalization costs per hospital per year with the addition of MDW to current SOC. In addition to the annual cost savings, MDW + SOC could potentially reduce ~10 in-hospital deaths per year and ~304 days in the hospital per year for sepsis-related hospitalizations.

Scenario Analyses

The scenario analysis results were recalculated by varying model inputs, including the time it would take for healthcare providers to obtain the MDW test result, the size of the hospital and the equations used to estimate the relationship between TTA and mortality and LOS. A summary of the scenario analyses is presented in **Table 5**. On a per-patient level, the cost offsets for the 45- and 60-minute intervals would be $3,166 and $2,889, respectively. At

TABLE 4. Results of Monocyte Distribution Width + Standard of Care Versus Standard of Care: Per Patient Per Sepsis Hospitalization

Outcome	Monocyte Distribution Width + SOC	SOC	Absolute Reduction
Inpatient mortality rate (%)	27.9	32.5	4.6 points
Mean length of stay (d)	10.0	11.5	1.48
Mean cost per sepsis hospitalization	$23,466	$26,926	$3,460

SOC = standard of care.

TABLE 5. Scenario Analyses

Variable	Value	Source	Absolute Reduction
Time to monocyte distribution width test			
Base case	30 min	Assumption	$3,460 per patient
Scenario analysis number 1	45 min	Assumption	$3,166 per patient
Scenario analysis number 2	60 min	Assumption	$2,889 per patient
Hospital size			
Base case	206 sepsis hospitalizations annually	Healthcare Cost and Utilization Project (26) American Hospital Association (28)	$712,783 per hospital
Small hospital (< 100 beds)	108 sepsis hospitalizations annually	Healthcare Cost and Utilization Project (26) American Hospital Association (28)	$373,692 per hospital
Large hospital (≥ 500 beds)	1,024 sepsis hospitalizations annually	Healthcare Cost and Utilization Project (26) American Hospital Association (28)	$3,543,153 per hospital
Mortality rate			
Base case	$y = 0.0241x + 0.2291$	Ferrer et al (23)	$3,460 per patient
Severity-adjusted mortality rate from Ferrer et al (23)	$y = 0.0143x + 0.2279$	Ferrer et al (23)	$2,016 per patient
Severity-adjusted mortality rate from Seymour et al (29)	$y = 0.0043x + 0.2269$	Seymour et al (29)	$234 per patient

the hospital level, the results suggest the annual per hospital savings associated with 45 and 60 minutes would be $652,204 and $595,112, respectively.

When evaluating hospital size, it was estimated that small hospitals would see offsets of $373,692 per hospital per year as well as a reduction in ~5 in-hospital deaths and 159 days in the hospital per year. Large hospitals would see offsets of $3,543,153 per hospital per year as well as a reduction in ~47 in-hospital deaths and 1,511 days in the hospital per year.

When utilizing severity-adjusted mortality data to estimate the relationship between mortality and TTA, the mortality rate for SOC was 28.5% and 24.4% when using Ferrer et al (23) and Seymour et al (29), respectively. The use of MDW + SOC was estimated to have an absolute reduction of 2.7% and 0.8% reduction, respectively. By applying the same relative reduction to the LOS, the patient-level cost offsets using MDW + SOC versus SOC would be reduced to $2,016 and $234 using the adjusted rates reported by Ferrer et al (23) and Seymour et al (29), respectively.

DISCUSSION

The results of this study suggest that MDW + SOC has the potential to improve the quality of care and would also reduce the costs of care provided to sepsis patients identified in the ED based on earlier sepsis detection and antibiotic treatment. Driven by innovative improvements in medical devices and diagnostics, payers and hospitals are increasingly interested in incorporating these improvements into their value-based purchasing decisions and utilizing evidence to support those decisions (30). At a hospital level, our model demonstrated that MDW resulted in ~$713,000 in annual savings. We recognize that a health system would require a DxH 900 instrument to provide the MDW test result. However, considering MDW can be included in a routine CBC-diff report (when requested by the ED physician according to its intended use), we chose to exclude any incremental costs of providing MDW in our model.

The potential reduction in LOS associated with MDW + SOC relative to SOC is another key point of value to facilities. Hospitals that can better manage sepsis patients will be able to reduce the number of days required to stay in the hospital. Given the time-sensitive nature of sepsis recognition and the impact of escalating care on increasing LOS, earlier screening for sepsis with MDW in this model resulted in a meaningful reduction in the estimated LOS. Not considered in this analysis was the potential for hospitals to improve bed turnover and related cost efficiencies through shorter LOS. This analysis also suggests there is a potential opportunity to reduce the in-hospital mortality rate among sepsis patients. Lower hospital mortality rates are tracked by insurers and are publicly reported, adding further value in terms of insurance compensation and hospital reputation.

In comparison to other methods commonly used to identify sepsis patients more quickly, MDW has obvious advantages. For example, procalcitonin has been explored as a biomarker for sepsis diagnosis (31). The results of two recent procalcitonin meta-analyses suggest there is uncertainty surrounding its diagnostic accuracy and reliability (32, 33). Further, there is limited evidence surrounding its health economic value to hospitals (34). And in contrast to MDW, procalcitonin is not routinely available to healthcare providers during the initial patient encounter. Procalcitonin

is not routinely used in the ED setting for the early identification of sepsis, but rather is used to validate the "clinical suspicion" of sepsis. Furthermore, procalcitonin does not typically guide initial treatment decisions for sepsis (e.g., antibiotics), which are often administered in the ED before the results of procalcitonin are available. As such, procalcitonin results do not influence initial diagnosis or treatment of sepsis, although procalcitonin may be useful for excluding sepsis and for discontinuing unnecessary antibiotic treatments (35). CDS tools, including alerts integrated into electronic health records (EHRs) systems, protocols, and algorithms, have been broadly and variably implemented at facilities in an effort to improve sepsis identification (15, 19, 20, 36, 37). Despite evidence that these tools have improved sepsis identification after patients have been admitted to the hospital (19, 20, 38), there is little evidence of their ability to significantly reduce TTA (20, 38–40), and the reliance on trends in EHR data limits CDS utility during the initial ED patient evaluation. Evidence also suggests that the implementation of CDS tools has often resulted in nonsignificant results in improving mortality (20, 38–40). Further, these tools have not been extensively evaluated from a health economic value perspective (37, 41). Calvert et al (37) found that the adoption of an algorithm-driven sepsis prediction system resulted in a reduction of about $560K in annual costs. Due to the dearth and heterogeneity of the evidence, a recent systematic review concluded that the current performance of automated sepsis support tools support the need for additional research (42).

There are limitations associated with this study that should be noted. Because the pivotal trial was noninterventional, the impact of MDW was simulated based on model assumptions. It was assumed that it would take 30 minutes from phlebotomy to availability of MDW results, that the clinician would act immediately on the results, order, and administer antibiotics to the patients. However, our scenario analyses suggest there is still a health economic benefit when assuming it would take 45 or 60 minutes to receive the MDW result. Furthermore, our study only included individuals who were ultimately diagnosed with sepsis. As such, the generalizability of our findings may be limited. Sepsis-2 criteria were used for sepsis detection in the pivotal trial, and these patients have better outcomes compared with the newer Sepsis-3 definition of sepsis. However, the Sepsis-2 patient population was enriched for more acutely ill patients based on the exclusion of those who were discharged from the ED within 12 hours in the pivotal trial. As a testimony to the high acuity of illness of patients enrolled in the pivotal study, a significant fraction (~15%) of ED patients presenting with infections did not fulfill sepsis criteria at the time of ED admission but progressed to Sepsis-3 within 72 hours of ED admission. Presumably, these patients would have benefitted from earlier sepsis detection and treatment. Although recent evidence suggests that TTA is an important determinant of health outcomes, there is variability in the evidence surrounding this relationship (43). Finally, there are study limitations that would contribute to the underestimation of the cost benefits to the insurance industry: most notably, earlier sepsis treatment is predicted to reduce the reliance on post-hospital healthcare due to improved health outcomes.

CONCLUSIONS

The results of this counterfactual clinical and economic analysis suggest that the novel, innovative biomarker, MDW, has the potential to provide added clinical and health economic value among sepsis patients presenting to the ED, a population with a well-established significant clinical and economic burden to patients and hospitals in the United States each year. Further research is warranted to confirm the actual reduction in TTA when MDW is used in real-world settings.

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